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CHRONIC LYMPHATIC LEUKEMIA ASSOCIATED WITH EXTENSIVE AMYLOIDITIS, ADVANCED NEPHRITIS AND ORAL SEPSIS.

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The following case is of particular interest, because it exemplifies one of the more unusual conditions which occasionally are associated with leukemia—namely, amyloid infiltration of the viscera in conjunction with an advanced nephritis. The patient was admitted to the medical service of Dr. Leroy H. Briggs at the San Francisco City and County Hospital, and I am indebted to Dr. Briggs for the following clinical history.

Case History. The patient was a married woman, aged forty-eight years, of American birth, who entered the hospital in April, 1920, complaining of chronic bronchitis. The family history and the past history were unimportant. The present illness dated from 1917, when she was treated at the Lane Hospital for leukemia. The following data, covering a period from November, 1917 to July, 1918, were obtained from the records of the Lane Hospital. The first recorded blood examination was made in the out-patient department on November 6, 1917:

Hemoglobin, 55 per cent. Red blood cells, 2,230,000. White blood cells, 10,000.

Differential count: Polymorphonuclear neutrophils, 34 per cent.; large mononuclears, 5 per cent; small mononuclears, 5 per cent; polymorphonuclear eosinophils, 1 per cent; polymorphonuclear basophils, 1 per cent; myelocytes, 3 per cent. One normoblast was present.

On entrance to the Lane Hospital in December, 1917, the outstanding findings were as follows: The patient was very pale; there was a loud blowing systolic murmur heard all over the precordium, although there were no palpable peripheral lymph nodes; the spleen was definitely enlarged and hard, extending well below the costal margin on the left to within 1 cm. of the umbilicus. The urine showed a large quantity of albumin and some hyaline casts. The phthalein test for renal function showed an output of 35 per cent of the dye in two hours. There was no Bence-Jones proteinuria. The subsequent findings and procedures in the Lane Hospital were as follows:

December 5, 1917. Blood examination: Hemoglobin, 50 per cent; red blood cells, 1,885,000; white blood cells, 25,300.

The differential count showed 71.5 per cent of lymphocytes with 3.5 per cent of myelocytes.

Between December 14 and June 1 the patient was given thirty-five roentgen-ray treatments over the spleen.

February 12, 1918. Blood examination: Hemoglobin, 55 per cent; red blood cells, 3,170,000; white blood cells, 38,000.

The differential count showed 80 per cent lymphocytes with 3.5 per cent myelocytes. The Wassermann reaction in the blood serum was negative. The stool examination and the gastric analysis showed nothing pathological.

July 29, 1918. Blood examination: Hemoglobin, 60 per cent; red blood cells, 3,810,000; white blood cells, 15,000.

The differential count showed 50 per cent lymphocytes and no myelocytes. The patient was discharged shortly after the last blood examination and appeared subjectively much improved. The discharge diagnosis was chronic lymphatic leukemia and mitral insufficiency.

Between this time and her admission to the San Francisco City and County Hospital in April, 1920, she appears to have been in at least fair health. On her admission to the last-named institution her chief complaint was chronic bronchitis. On physical examination the following essential points were noted:

The patient is a middle-aged woman with marked pallor of the skin and mucous membranes. There are a few purpuric spots over the forearms. There is extreme dental caries and pyorrhea alveolaris. The heart is not enlarged. There is a loud, blowing, systolic murmur over the precordium, maximal at the apex. The peripheral vessels are not palpable. The blood-pressure is 130 systolic over 45 (?) diastolic. The spleen is large, firm and found well below the left costal margin almost to the umbilicus. The liver is not palpable. The urine examination shows a urine of low specific gravity, 1.005. No sugar or Bence-Jones proteinuria are found. Albumin is present in large quantities and many finely granular and hyaline casts. The phthalein test for kidney function shows

almost complete suppression of the dye in the usual two-hour period —there is less than 5 per cent recovered. The urine collected at two-hour intervals during the day and over the whole nocturnal period after the manner of the Mosenthal renal test diet plan for the estimation of the renal function showed a definite fixation of the specific gravity at 1.005 in all the specimens in conjunction with nocturnal polyuria.

Blood examination: Hemoglobin, 20 per cent; red blood cells, 2,024,000; white blood cells, 15,000.

The differential count showed: Polymorphonuclears, 20 per cent; large mononuclears, 6 per cent; small mononuclears, 71.6 per cent; polymorphonuclear basophils, 14 per cent; polymorphonuclear eosinophils, 0; neutrophilic myelocytes, 1.6 per cent.

The blood platelets appeared decreased in number and no normoblasts were seen. There was no poikilocytosis or anisocytosis. During her subsequent course in the hospital the blood picture remained essentially the same as the above outlined count, except for a terminal myelocytic increase to 8 per cent.

On account of the extreme oral sepsis an attempt was made to have the mouth cleaned up by the removal of carious teeth. Following the dental extractions, severe bleeding ensued, which continued for several weeks immediately prior to the patient's death on November 5, 1920.

The salient features of the gross pathology, as revealed by the necropsy performed by Dr. W. A. Perkins, were as follows:

There was a moderate amount of subcutaneous tissue present which was hyperchromatic in color. The heart was slightly enlarged with a normal appearing myocardium. The spleen was considerably enlarged and weighed 250 gm. The capsule was markedly thickened and the surface was smooth and glistening. On section the spleen was found to be firm in consistence and the pulp did not scrape off readily. The liver was not enlarged and showed nothing remarkable on cut section, except that it was pale in color and had a greasy, lardaceous appearance. The kidneys were of equal size, not enlarged, and they presented the same greasy appearance as the cut surface of the liver. The kidney capsules stripped readily and there was no increase of pelvic fat. On section the renal cortex of both kidneys was found to be contracted. The glomeruli were visible as definite white points. On frozen section the glomeruli appeared as homogeneous, solidly acid-staining balls, whereas the renal arteries were encircled by homogeneous, acid-staining material. The bone-marrow obtained from the femur was of a brownish-red color and appeared distinctly increased in amount. The iodine reaction for amyloid was definitely obtained on sections of tissue from the liver, spleen, kidneys and adrenals.

The microscopical study of the tissues confirmed the impression that we were dealing with an extensive amyloidosis of the viscera, and briefly added the following facts:

In the liver the intermediary zone was occupied by an almost complete replacement of the liver cells by a homogeneous staining, structureless material. The spleen showed areas of infiltration of mononuclear cells in great numbers. The Malpighian bodies were less infiltrated with the amyloid than the surrounding structures. The kidneys presented a striking microscopical picture, revealing the lesions of an advanced, diffuse, chronic nephritis in association with an extensive amyloid infiltration. The glomeruli were very prominent and appeared as solidly, acid-staining balls. In many places glomerular adhesions to Bowman's capsule could be made out. The other renal vessels were also involved in the amyloid process and showed a definite replacement of their muscular coat with the waxy, homogeneous, acellular material. The adrenals also presented in an exquisite manner the same amyloid infiltration as noted in the foregoing organs. Another prominent feature of the microscopical study was the presence in all the viscera of clumps of small round mononuclear cells deep in the tissues and usually surrounding the capillaries. The bone-marrow was clearly hyperplastic and the mononuclear elements definitely dominate the cellular picture.

Comment. The above case gives rise to several interesting questions which cannot be wholly explained or answered. In the first place, is there any relationship between the leukemia and the amyloidosis? Osler[1] mentions the fact that leukemia is one of the less usual disease conditions in which amyloid infiltration of the viscera is occasionally encountered. Ordway and Gorham,[2] in their recent excellent discussion of the leukemias in *Oxford Medicine*, do not mention amyloidosis as even an occasional pathological finding in leukemia. Amyloidosis is established as associated with chronic suppuration, and consequently is found in tuberculosis, particularly tuberculous osteomyelitis; empyemas of long standing and syphilis. Among the other less common conditions in which it occurs are malarial cachexia, lead-poisoning, carcinoma and leukemia.

Experimentally amyloidosis has been produced in various ways. One of the most successful recent researches is that of Bailey,[3] who produced visceral amyloidosis in rabbits by the injection of cultures of the living colon bacillus over long periods. Hirose,[4,5] working in Welch's laboratory on a similar problem, failed to produce amyloid disease artificially in goats, dogs and rabbits by using

[1] Principles and Practice of Medicine, 1912, 8th ed., p. 711.

[2] Oxford Medicine, Christian and Mackenzie, 1920, 2, 681.

[3] The Production of Amyloid Disease and Chronic Nephritis in Rabbits by Repeated Intravenous Injections of Living Colon Bacilli, Jour. Exp. Med., 1916, 23, 773.

[4] Experiments in the Artificial Production of Amyloid, Johns Hopkins Hosp. Bull., February, 1918, 29, 40.

[5] The Blood-pressure in Amyloid Kidney Disease, Johns Hopkins Hosp. Bull., August, 1918, 29, 191.

subcutaneous injections of cultures of Staphylococcus aureus and turpentine. He concluded, "That the artificial production of amyloid is very difficult and inconstant, even when methods are employed which have sometimes been successful." The same investigator points out from a study of 59 cases of amyloid kidney disease collected from the pathological records of Johns Hopkins and the Bay View Hospitals of Baltimore that in every case studied there was a trace of nephritis with degenerative changes in the renal epithelium of the tubules and scarring of the more affected areas. He believes, although he could not prove it, that the amyloid infiltration itself plays little part as a causative factor in the associated nephritis, and he is inclined to think that the factor which caused the presence of the amyloid is also capable of producing the changes in the kidney substance—in other words, the nephritis. In view of this, those who are adherents of the infectious hypothesis for the etiology of leukemia may find a common explanation of the two conditions in the above case. Furthermore, Hirose made some interesting observations in regard to the blood-pressure in a certain number of the cases he studied. In 15 cases of definite kidney disease in which blood-pressure determinations had been made it was found to be normal or below normal.

A second point for consideration is, what if any relationship existed between the marked oral sepsis which was present over a long period, the amyloidosis, the leukemia with splenomegaly but without generalized lymphatic enlargement, and the advanced nephritis? In a cursory review of the literature I have found no reference to oral sepsis in relation to amyloidosis—obviously our case throws no light on this point. In regard to oral sepsis in association with blood diseases such as anemias, including both the primary and the secondary types, numerous writers have emphasized a frequent clinical concomitance. If any fundamental relationship does exist with the anemias, would it be unreasonable to think that some such relationship might also be present with leukemias?

The inference of a causative connection between oral sepsis and chronic nephritis has been extensively alluded to in the recent medical writing, and will only be mentioned here.

In conclusion the question may be raised by the above case as to whether we are dealing with a true lymphatic leukemia or merely an extreme grade of lymphocytosis in the presence of a chronic infection. Cabot[6] called attention to three groups of cases in which the diagnosis between lymphatic leukemia and the simple lymphocytosis may be in doubt—namely, in pneumonia; following wound sepsis; and finally subsequent to tonsillitis which was accompanied by a general lymphoid enlargement. In all of these condi-

[6] Modern Medicine, Osler and McCrae, 1913, 4, 676.

tions he has seen a lymphocytosis of such an extreme grade that a true lymphatic leukemia was difficult to exclude. Quite recently Sprunt and Evans[7] have also called attention to another group of cases occurring in young adults in which there is found a mononuclear leukocytosis accompanying an acute infection. They point out that this type of case may be difficult to distinguish at times from the onset of an acute leukemic state or of an early Hodgkin's disease. It accompanied upper respiratory infections, and particularly tonsillitis, and in 4 of their 6 cases it was associated with a moderate grade of general glandular enlargement. The blood picture showed a slight increase in the cells of the large mononuclear-transitional group and the presence of many pathological lymphoid forms. All of these cases went to complete recovery, with the return of the differential formula to normal limits.

Obviously, our case cannot be classed with these last-mentioned groups of Cabot and Sprunt and Evans. The only clinical point against the diagnosis of chronic lymphatic leukemia was the persistent absence of general glandular enlargement. The long clinical course of our case, extending as it did over a period of three years, the constant presence of splenomegaly and the study of the necropsy material, with special reference to the bone-marrow, left little doubt that the case was primarily a true instance of chronic lymphatic leukemia with the rather unusual association of extensive amyloidosis and advanced nephritis.

[7] Mononuclear Leukocytosis in Reaction to Acute Infections. ("Infectious Mononucleosis"). Johns Hopkins Hosp. Bull., 1920, 31, 410.